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(54) [Title of the Invention] Tissue Marker

(57) [Abstract]

[Object] An object is to provide a tissue marker to conduct surgery accurately by reliably locating the resection site in surgical resection procedures not associated with laparotomy or thoracotomy.

[Constitution] A tissue marker composed of a stain and a material that resists diffusion and is biocompatible.

[Claims]

[Claim 1] A tissue composed of a stain and a material that resists diffusion and is biocompatible.

[Claim 2] The tissue marker of Claim 1, wherein the material that resists diffusion and is biocompatible is a solution or dispersion.

[Claim 3] The tissue marker of Claim 1, wherein the material that resists diffusion and is biocompatible is collagen, gelatin, agarose, fibrinogen-thrombin, polysaccharide-calcium salt, cyanoacrylate, or a mixture of substances selected from the group thereof.

[Claim 4] The tissue marker of Claim 1, wherein the material that resists diffusion and is biocompatible is mixed with a contrast medium.

[Detailed Description of the Invention]

[0001]

[Field of Industrial Utilization] The present invention relates to a tissue marker intended to make it possible to verify the resection site with the naked eye by marking the resection site beforehand in surgical resection procedures and diagnoses not associated with laparotomy or thoracotomy.

[0002]

[Prior Art] The utilization of surgical procedures not associated with laparotomy or thoracotomy using an endoscope (such as a laparoscope or thoracoscope) has expanded in recent years, and such procedures have come to be utilized frequently in diagnosis and treatment. For example, one method of diagnosis and treatment of a disease is to study the tissues and organs by x-rays, CT, and the like and to sample the tumor tissue by a surgical resection procedure if a suspected lesion is detected. Use of an endoscope in this resection procedure has advantages such as creating a smaller surgical wound than in ordinary surgery and reducing the burden placed on the patient. However, it is extremely difficult to accurately verify the resection site with the naked eye by using an endoscope. When the tumor is small in particular, samples are sometimes taken from erroneous locations if the location of the tumor is not accurately verified. In this case, the pathological tissue cannot be sampled again due to damage to the surrounding tissue, and great harm is done to diagnosis and treatment, such as making the tumor impossible to diagnose pathologically. Given such significant problems, surgical resection of a lesion using an endoscope is often avoided despite its many advantages, and resection is frequently performed by laparotomy or thoracotomy. However, such surgery is extensive, the surgical wound is large and takes a long time to heal, adhesions tend to develop due to contact with air, and other problems are encountered. A method of marking the location prior to surgery using a hook-wire (R. M. Shah et al., A.J.R., 161 279 (1993)) exists for small lung tumors. However, this method is disadvantageous in that it always results in pneumothorax, and imposes a heavy burden on the patient. A method of marking the location by a stain after verifying the lesion by CT has been proposed recently to resolve such drawbacks (Stephan Wicky et al., CHEST, 106(5), pp. 1326-1328 (November, 1994)). However, since the stain diffuses within 3 hours when the location has been marked by a solution obtained by adding the stain to physiological saline, the coloring has spread over a wide region by the time of surgery even when marking is performed immediately before surgery. The location of the lesion becomes unclear, the coloring fades, and clinical use becomes practically impossible.

[0003]

[Problems to be Resolved by the Invention] As a result of studies conducted in view of the above situation and aimed at resolving such problems, the inventors perfected the present invention upon discovering that the stain becomes resistant to diffusion, fading is slowed, and the mark remains until the time of surgery up to approximately 1 week later when the stain is mixed with a diffusion-resistant material and used as the marker. Therefore, an object of the present invention is to provide a tissue marker to accurately perform surgery by reliably locating the resection site in surgical procedures not associated with laparotomy or thoracotomy.

[0004]

[Means of Problem Resolution] The essence of the present invention is a tissue marker composed of a stain and a material that resists diffusion and is biocompatible. This tissue marker may also be mixed with a contrast medium. Specifically, the tissue marker of the present invention can suppress fading within the tissue by mixing the stain with a material that resists diffusion and is biocompatible, and can be used effectively in observation in surgical resection procedures with an endoscope 1 week after staining.

[0005] The present invention will be discussed in detail below. The tissue marker of the present invention is prepared by mixing a stain and a material that resists diffusion and is biocompatible. Although no particular limitation is imposed, the tissue marker preferably has a pH of 4–9. The stain that can be used in the present invention is not particularly limited as long as it is a stain that is permissible for use in the body. Methylene blue, diazo green, and the like are preferred. The concentration of the stain is not particularly limited, but is preferably 10–300 mg/mL. A certain degree of fading is seen after 1 week owing to the small quantity of stain when the concentration is less than 10 mg/mL. This can sometimes make it difficult to verify the stained location clearly by the naked eye. At the other extreme, the stain becomes difficult to dissolve when the concentration is more than 300 mg/mL.

[0006] Examples of material that resist diffusion and are biocompatible include collagen, gelatin, agarose, fibrinogen-thrombin, polysaccharide-calcium salt, cyanoacrylate, and mixtures thereof. However, the materials are not limited to these. These materials are generally substances with high viscosity, which makes it possible to prevent diffusion of the stain. A contrast medium can also be mixed with the material that resists diffusion and is biocompatible. Using a contrast medium in the

mixture makes it possible to mark the target site even more accurately.

[0007] The tissue marker of the present invention is obtained by adding a prescribed amount of a dissolved or dispersed material that resists diffusion and is biocompatible, and mixing it with the stain. For example, when collagen is used as the biocompatible material, the collagen is obtained from animal skin, tendons, or the like. It may be either solubilized collagen or insolubilized collagen if it is purified. Examples of solubilized collagen include acid-solubilized collagen, salt-solubilized collagen, enzyme-solubilized collagen, alkali-solubilized collagen, and chemically modified collagen (such as succinylated, phthalated, acylated, and methylated collagen). Examples of insolubilized collagen include Achilles tendon collagen, hide collagen, fibrous collagen, and crosslinked collagen. This collagen is used as a solution or dispersion in a concentration of about 1 mg/mL to 70 mg/mL. No effect can be expected below 1 mg/mL, while injection into the tissue by a syringe needle or the like is difficult above 70 mg/mL.

[0008] Examples of the gelatin include acid-solubilized and alkali-solubilized gelatin. In the case of gelatin and agarose, the concentration of the solution or dispersion is preferably about 5-300 mg/mL. A solution or dispersion of such a concentration liquefies above 40°C and gels when lowered to body temperature. Fibrinogen-thrombin can also be gelled by utilizing the coagulation reaction of fibrinogen. Products such as Tisseal (Immuno), Beriplast (Hoechst), and Bolheal (Kaketsuken) can be used. A fibrinogen concentration of 10-200 mg/mL and a thrombin concentration of 4-500 IU (where IU is "international units") are preferred for the concentration of the fibrinogen-thrombin. Examples of the polysaccharide in the case of a polysaccharide-calcium salt solution include alginic acid, pectin, and mannan. This solution or dispersion can be gelled by being mixed with a calcium salt such as calcium chloride. The concentration of the polysaccharide is preferably 1–300 mg/mL, and the calcium concentration is preferably about 10–100 mg/mL.

[0009] The tissue marker based on the present invention is injected into the tissue using a syringe needle or the like to stain the tissue. For example, contrast medium is injected from a syringe containing the contrast medium through the syringe needle, the lesion is identified by CT, the syringe is switched for one that contains the tissue marker (with the syringe needle remaining in place), and the tissue is stained by injection into the site of the lesion. The lesion is thus stained in a reliable manner by tissue marker, and the pathological tissue can be reliably sampled thereafter by a surgical resection procedure using an endoscope. Concrete working examples appear below. However, the method for using the tissue marker of the present invention is not limited to these examples alone.

[0010]

[Working and Comparative Examples]

Working example 1

Methylene blue was mixed with a concentrated neutral physiological saline of atelocollagen (30 mg/mL Koken atelocollagen implant) to a concentration of 10.0%, and 1.0 mL was injected through a syringe needle into the lungs of rabbits (male, 10 weeks old). When the animals were thoracotomized 1 week later and their lungs were removed and examined, the stain remained at an intensity that would permit observation with an endoscope, and staining was understood to have been effective.

[0011] Comparative example 1

Methylene blue was mixed with physiological saline to a concentration of 10.0%, and 1.0 mL was injected through a syringe needle into the lungs of rabbits (male, 10 weeks old). The next day, the urine was stained blue and it was assumed that the stain was being excreted from the body. The animals were thoracotomized 24 hours later and their lungs were removed and examined, but it was impossible to verify the stained location or to maintain staining for 24 hours.

[0012] Working example 2

Agarose was mixed with physiological saline to a concentration of 100 mg/mL and dissolved by heating. Methylene blue was mixed with the product to a concentration of 10.0%, and 1.0 mL was injected through a syringe needle into the lungs of rabbits (male, 10 weeks old). When the animals were thoracotomized 1 week later and their lungs were removed and examined, the stain remained at an intensity that would permit observation with an endoscope.

[0013]

[Merits of the Invention] As has been discussed above, the present invention is a tissue marker composed of a stain and a material that resists diffusion and is biocompatible. Since fading can be controlled and the stain remains even when surgery is performed 1 week after staining, the lesion can be verified macroscopically and the pathological tissue can be sampled in a reliable manner. This makes it possible to conduct surgery in a reliable manner without the accompanying laparotomy or thoracotomy by making use of an endoscope, which provides numerous advantages.

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